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Volatile Hydrocarbon Exposures and Incident Coronary Heart Disease Events: Up to Ten Years of Follow-up among *Deepwater Horizon* Oil Spill Workers

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Background: During the 2010 *Deepwater Horizon* (*DWH*) disaster, response and cleanup workers were potentially exposed to toxic volatile components of crude oil. However, to our knowledge, no study has examined exposure to individual oil spill–related chemicals in relation to cardiovascular outcomes among oil spill workers.

Objectives: Our aim was to investigate the association of several spill-related chemicals [benzene, toluene, ethylbenzene, xylene, *n*-hexane (BTEX-H)] and total hydrocarbons (THC) with incident coronary heart disease (CHD) events among workers enrolled in a prospective cohort.

Methods: Cumulative exposures to THC and BTEX-H across the cleanup period were estimated via a job-exposure matrix that linked air measurement data with self-reported *DWH* spill work histories. We ascertained CHD events following each worker's last day of cleanup work as the first self-reported physician-diagnosed myocardial infarction (MI) or a fatal CHD event. We estimated hazard ratios (HR) and 95% confidence intervals for the associations of exposure quintiles (Q) with risk of CHD. We applied inverse probability weights to account for bias due to confounding and loss to follow-up. We used quantile g-computation to assess the joint effect of the BTEX-H mixture.

Results: Among 22,655 workers with no previous MI diagnoses, 509 experienced an incident CHD event through December 2019. Workers in higher quintiles of each exposure agent had increased CHD risks in comparison with the referent group (Q1) of that agent, with the strongest associations observed in Q5 (range of HR = 1.14–1.44). However, most associations were nonsignificant, and there was no evidence of exposure–response trends. We observed stronger associations among ever smokers, workers with ≤high school education, and workers with body mass index $<30\,kg/m^2$. No apparent positive association was observed for the BTEX-H mixture.

Conclusions: Higher exposures to volatile components of crude oil were associated with modest increases in risk of CHD among oil spill workers, although we did not observe exposure–response trends. https://doi.org/10.1289/EHP11859

Introduction

The 2010 *Deepwater Horizon* (*DWH*) disaster was the largest marine oil spill in U.S. history.[1] An estimated 4.9 million barrels of crude oil were discharged into the Gulf of Mexico before the wellhead was mechanically capped on 15 July 2010.[1] Shortly after the spill began, an extensive oil spill response and cleanup (OSRC) operation was launched to stop the spill and remove the crude oil from the environment. Tens of thousands of workers and volunteers participated in this operation, with most efforts completed by June 2011.[2]

During the OSRC, workers were exposed to a range of inhalation hazards, including volatized crude oil hydrocarbons.[3] These hydrocarbons were a significant contributor to air emissions in the *DWH* disaster.[4] Many of these components, including benzene, some alkylbenzenes, and hexane, are classified as hazardous air pollutants because of their toxicological properties.[5] Studies have associated short-term ambient exposure to benzene and alkylbenzenes with acute onset of myocardial infarction (MI)[6] or coronary death.[7,8] Chronic benzene exposure has also been linked to persistent MI mortality in a Spanish case–control study; however, the study failed to account for important confounders, including smoking and socioeconomic status.[9]

Persistent respiratory effects have been observed among workers who participated in various oil spill cleanups[10–13]; however, associations between OSRC-related exposures and cardiovascular health were previously assessed only in workers who responded to the *Hebei Spirit* oil spill and the *DWH* disaster.[14–17] In an analysis of *Hebei Spirit* oil spill workers, longer duration of cleanup work was associated with higher risk of self-reported angina or MI up to 10 y after the spill. In the *DWH* disaster, Strelitz et al.[16] observed higher incidence of self-reported MI or fatal coronary heart disease (CHD) up to 5 y after the spill among OSRC workers with longer duration of work and with higher single daily maximum exposure to total (petroleum) hydrocarbons (THC), a composite measure of volatile components of the crude oil.[17] Similar associations were found when nonfatal MI was examined as the outcome.[15]

These studies provide some evidence that exposure to crude oil chemicals may be related to increased risk of MI/coronary heart disease (CHD) over time. Recently, quantitative estimates

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of several cumulative oil-related exposures [THC, benzene, toluene, ethylbenzene, xylene (all isomers combined), and *n*-hexane (BTEX-H)] were developed from personal measurements and self-reported OSRC activities for the *DWH* OSRC workers,[18] providing an opportunity to study health effects associated with these specific chemical exposures among the same group of workers and with several additional years of follow-up. Given that BTEX-H also arise from a single emission source in other environments (e.g., vehicular exhaust, oil/gas operations),[19,20] it is useful to assess the joint effect of the exposure mixture to support interventions that target the exposure source. The objective of this study was to assess quantitative oil-related exposures, individually and as a mixture, in relation to incident CHD events among *DWH* OSRC workers.

Methods

Study Population

The GuLF Study (Gulf Long-Term Follow-up Study) is a prospective cohort study of the potential health effects of the *DWH* disaster.[3] Participants included anyone ≥21 y of age at enrollment who either had participated in OSRC work for at least 1 d (workers) or had completed safety training but were not hired (nonworkers). Enrollment started in March 2011 and continued through May 2013. A total of 32,608 participants were enrolled. At enrollment, all participants completed a computer-assisted telephone interview in which they provided information on sociodemographics, lifestyle, health (including physician diagnosis of MI), and a detailed history of *DWH* OSRC activities. Two rounds of follow-up interviews (May 2013–Apr 2016 and November 2017–July 2021) were conducted via telephone to ascertain changes in health status (including new physician diagnoses of MI) since the previous interview. We excluded from the current analysis 999 Vietnamese-only speaking participants who completed only an abbreviated enrollment interview that precluded ascertainment of MI diagnosis or estimation of oil spill-related chemical exposures.

For all analyses, we restricted the study population to the 24,375 workers; we restricted our analysis to participants who worked at least 1 d on the *DWH* cleanup ("workers") because they had the opportunity to be exposed to crude oil chemicals.[3] We excluded 21 workers who did not provide information on MI diagnoses in any of the interviews. We restricted our analysis to incident cases by beginning follow-up at the end of each worker's cleanup work time and excluded 489 workers who reported an MI diagnosis before the start of follow-up. Although reports of MIs that occurred during cleanup would be informative, it is also likely that workers who had such an event might have stopped working and were not enrolled in our study; thus, including the person-time before the end of cleanup could lead to immortal time bias. Of the remaining 23,865 workers, we restricted our analysis to 23,664 workers who had complete THC and BTEX-H exposure estimates. Finally, we excluded 1,009 workers with missing covariates needed for analysis and reached a final analytical sample of 22,655 workers. Figure S1 illustrates how we derived the analytical sample from the enrolled population. Among these participants, 15,627 (69%) and 10,638 (47%) completed the first and second follow-up interviews, respectively. Response rates were over 88% in both follow-ups among those who could be reached. All participants provided informed consent prior to participating in the GuLF Study. The institutional review board of the National Institute of Environmental Health Sciences approved this study.

Exposure Assessment

Cumulative exposures to five spill-related chemicals (BTEX-H) and THC across each participant's work period were estimated via a job-exposure matrix that linked air measurement data with detailed work histories. Measurement data came primarily from ∼28,000 full-shift personal air samples collected on OSRC workers using organic vapor passive dosimeters during their work shifts from April 2010 to June 2011.[18] These samples were analyzed for THC and BTEX-H, resulting in more than 143,000 measurements of THC (as petroleum hydrocarbons) and BTEX-H.[18,21] These personal measurements were supplemented by more than 26 million direct-reading volatile organic compound (VOC) area measurements collected using multigas detectors (AreaRAE and MultiRAE) equipped with a photoionization detector lamp on 38 vessels involved in the OSRC to develop THC and BTEX-H estimates on days and vessels where there were few or no personal measurements.[22,23]

To estimate exposures for the full cohort, the study industrial hygienists created more than 3,000 exposure groups (EGs) based on three exposure determinants: job/activity, location, and time period.[24] Job was a major determinant of exposure, but because job title [e.g., crane operator, remotely operated vehicle (ROV) technician] was not available for all workers, industrial hygienists supplemented job title information with self-reported work activities (e.g., handling oily boom, skimming, decontamination) to develop this exposure determinant. Location covered four areas of the Gulf (by increasing distance from the wellhead: hot zone/source, offshore, nearshore, land) and four Gulf coastal states (Louisiana, Mississippi, Alabama, Florida). The OSRC work period (22 April 2010–30 June 2011) was divided into seven time periods: TP1a (22 April–14 May 2010), TP1b (15 May–15 July 2010), TP2 (16 July–10 August 2010), TP3 (11 August–30 September 2010), TP4 (1 October–31 December 2010), TP5 (1 January–31 March 2011), and TP6 (1 April–30 June 2011). These time periods were developed to reflect changes in the degree of weathering of the oil (which increased over time) and in OSRC events that likely affected workers' exposures. For instance, the mechanical capping of the wellhead on 15 July 2010, which separated TP1b and TP2, marked the stop of oil release from the damaged well and the end of oil/gas flaring and dispersant application operations. For a detailed explanation of the criteria used to define each time period, see Stewart et al.[18] Each EG was a unique combination of these determinants and represented workers who, based on these determinants, were expected to have similar distributions of exposures. Using these determinants, industrial hygienists assigned air measurements to each EG and estimated exposure averages for the EGs.[22,23,25–29] To handle the large number of measurements below the analytical method's limit of detection in some EGs, a left-censored Bayesian framework was used to estimate exposure averages and other exposure statistics for the EGs.[25,26]

Workers were matched to the appropriate EGs based on their reported *DWH* OSRC work history. Many workers reported multiple work activities across the cleanup, some of which occurred on the same day. Although workers reported the start date, end date, and days worked for each job/activity, we lacked information on the specific days and the exact number of hours on these days that they performed each job/activity. Thus, we developed two daily exposure estimates for each day worked: *a*) the daily maximum, the value corresponding to the highest-exposed activity on a day; and *b*) the daily average, the average of the exposure estimates across all jobs/activities on each day. To examine the total burden of exposure received by each worker during the cleanup, two cumulative exposure metrics were created across all workdays based on their daily exposure estimates and the duration of their work: *a*) cumulative daily maximum, the sum of daily maximum exposure estimates across all days within a time period and then across all time periods; and *b*) cumulative daily average, the sum of daily average exposure estimates across all

days within a time period and then across all time periods. These measures are the primary exposure estimates examined in the current analyses. We also considered as each worker's exposure the single highest daily maximum exposure estimate (henceforth, "single daily maximum" exposure) over the entire work period in a subanalysis. In secondary analyses, we explored the health impacts among workers who had multiple unusually high daily exposures to BTEX-H or THC by comparing them with workers who exclusively had only lower daily maximum exposure estimates (as described in the section titled "Statistical Modeling" below).

Outcome Assessment

The outcome of interest was the first occurrence of a CHD event after the last day of each participant's OSRC work, defined as either a self-reported physician-diagnosed MI or an *International Classification of Diseases* (ICD)–coded fatal CHD event. At enrollment and in the two follow-up interviews, participants were asked "Has a doctor ever told you that you had a heart attack, also called a myocardial infarction or 'MI'?" Those who responded "yes" were asked to provide the month and year of, or the age at, the event. Fatal CHD events were ascertained via linkage with the National Death Index through 31 December 2019, and we included deaths attributed to ischemic heart disease (ICD-10 code I20–I25) as an underlying cause. Time at risk was measured in months from the date after each participant ended cleanup work to the first of CHD event, death from other causes, end of cohort follow-up (31 December 2019), or, for participants who were lost to follow-up (i.e., did not respond to the first or both follow-up interviews and were event-free), the date they completed the previous interview.

Statistical Modeling

We used Cox proportional hazards models to estimate hazard ratios (HRs) for the first incident CHD event associated with increasing cumulative exposure to each BTEX-H chemical and THC.[30] We used quintiles of exposure levels for analysis, with workers in the lowest quintile (Q1) of an exposure agent as the referent group. We also investigated exposure–response trends by examining ln-transformed continuous exposure levels. We chose time since exposure, rather than age, as the time scale. Although age was an important confounder in our study, using it as the time scale would imply that workers who entered the study at an older age were exchangeable prior to study entry with workers who entered study at a younger age, given all confounders.[31] This assumption is not possible to verify with the data at hand.

We adjusted for potential confounding using inverse probability (IP) weighting.[32] We selected covariates based on a directed acyclic graph (DAG) and included the minimally sufficient adjustment set and predictors of the outcome that are not descendants of the exposure in the IP-exposure weights (Figure S2).[33–35] Because of high correlations among exposures (range: 0.84–0.96) (Table S1), we were not able to account for coexposures in the weights. We obtained stabilized weights by fitting a multinomial logistic regression model for each categorical exposure with respect to selected covariates. In analysis of ln-transformed continuous exposures, we generated weights for each exposure agent using a quantile binning approach.[36]

All covariates were self-reported or derived from information that was self-reported at enrollment and included the following: age (in years: 20–29, 30–39, 40–49, 50–59, ≥60), sex (male; female), race (White; Black; American Indian or Alaskan Native; Asian; Native Hawaiian or Pacific Islander; other race), Hispanic ethnicity (Hispanic; non-Hispanic), cigarette smoking status [current heavy (≥20 cigarettes/day); current light (<20 cigarettes/day); former; never], highest educational attainment (less than high school; high school diploma or general equivalency diploma; some college or 2-y degree; 4-y college graduate or more), body mass index [BMI, in kilograms per square meter: underweight or normal (<25); overweight (25 to <30); obese I (30 to <35); obese II (≥35)], previous oil spill cleanup experience (yes, no), previous oil industry experience (yes, no), precleanup diabetes diagnosis (yes, no), and residential proximity to the spill (living in a coastal county directly affected by the spill or a county adjacent to the impacted counties; living in a Gulf state farther from the spill; living in a non-Gulf state). We used self-reported race and ethnicity as proxies for the downstream effects of socioeconomic disparities as well as differential life experiences resulting from structural racism that might have influenced risk of CHD. For analysis, race was collapsed into White, Black, and "other/multiracial" because of the small number of participants who were not White or Black.

To account for informative censoring due to loss to follow-up, we used IP-censoring weighting.[37,38] Participants were considered censored if they *a*) did not complete a follow-up interview or completed the first but not the second interview and *b*) had not experienced a CHD event prior to being lost to follow-up. Censoring was modeled as a function of its predictors in a pooled logistic regression, and weights were stabilized by the marginal probability of censoring. Covariates in the IP-censoring weights were determined from a DAG[34] and included: exposure(s) (THC for model of THC; all chemicals of BTEX-H for each model of BTEX-H), age, sex, self-reported race, Hispanic ethnicity, cigarette smoking, highest educational attainment, previous oil spill cleanup experience, and residential proximity to the spill. The finalized weights applied to the models were the product of the IP-exposure weights and the IP-censoring weights. Cox proportional hazards models with a robust variance estimator were fitted to estimate HRs and 95% confidence intervals (CIs). IP-exposure weights and IP-censoring weights were applied to the main analysis and subanalyses.

In single-agent analyses, we investigated potential effect measure modification (EMM) by cigarette smoking status (ever vs. never), because smoking could induce adverse cardiovascular effects via biological pathways similar to those of air pollutants and thus enhance the effects of air pollutants, including the crude oil chemicals examined in our study.[39] We also examined EMM of the associations by educational attainment (high school or less vs. more than high school). Previous studies have shown stronger effects of ambient air pollution on CHD risk among study participants with lower educational attainment,[40,41] possibly because the adverse effects of air pollutant exposure were exacerbated by detrimental lifestyle (e.g., lack of access to healthy food, participation in less leisure time physical activity) and other environmental contaminants[42–44] associated with less educational attainment.[45–47] In addition, we stratified analyses by obesity [nonobese (BMI <30) vs. obese (BMI ≥30)] at enrollment to see whether there was heterogeneity among associations. As a major risk factor for cardiometabolic diseases, obesity could potentially increase air pollution–related health effects because of persistent obesity-induced low-grade inflammation[48] and higher particle deposition in the lung from higher breathing rates and tidal volumes among obese people.[49–51] We assessed EMM by including a product term between quintile exposure and the modifier in the model and reported the *p*-value for the joint Wald test. In addition, we examined associations between exposures and CHD risk in the subset of participants who were age 40 y and older. We were unable to examine associations in participants younger than age 40 y because of the small number of cases in this subgroup.

We conducted a number of sensitivity analyses. First, we included self-reported precleanup hypertension in the IP-exposure weight model to see whether results differed. This covariate was not included in the main analysis because precleanup hypertension was not related to crude oil exposures and we were concerned about possible misclassification of hypertension using self-reports.[52] We also accounted for several other *DWH* OSRC–related exposures that have been associated with CHD in other studies. To address potential confounding from exposure to higher levels of fine particulate matter (PM) with aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$) from controlled burning activities,[53,54] we reran the analysis excluding 1,997 workers with higher burning exposures. Because ever having to stop working during the cleanup because of heat (yes, no), a proxy for high heat exposure, was associated with higher risk of nonfatal MI in a previous GuLF Study analysis,[15] we included this variable in the weight model to determine whether it affected results. We also included in the model a variable for having performed any jobs during the cleanup that involved handling oily plants/wildlife or dead animal recovery (yes, no) to account for potential psychological stress from specific OSRC work that may have contributed to risk of CHD.[55] To assess whether our estimates were sensitive to how age was specified in the model, we investigated restrictive cubic splines as an alternative functional form of age. In addition, we conducted analyses using an alternative definition of CHD-related deaths based on ischemic heart disease as a contributing/underlying cause rather than the underlying cause of death. We attempted to examine nonfatal MI and fatal CHD as separate outcomes; however, we could not examine fatal CHD as the outcome because of the small number of fatal cases. Workers with fatal (CHD) events that occurred after OSRC employment but before they could enroll were not identified. We explored the impact of this left truncation in a sensitivity analysis by starting the risk period at study enrollment, effectively excluding 129 preenrollment MI events. To follow up on the analysis of Strelitz et al.,[17] which used an earlier, ordinal classification of the single daily maximum THC exposure and observed participants only through the first follow-up interview, we conducted a similar analysis using the newly developed quantitative single daily maximum THC exposure (categorized in quintiles) and observed participants for both the same and the extended time period (until December 2019). To explore the potential bias from inaccurate recall of the date of CHD diagnosis among participants who reported a nonfatal CHD event, we performed an exploratory analysis that coarsened the time interval in which events were identified so that CHD events were tallied every 4 months instead of every month. Last, to capture milder forms of CHD that could progress to MIs and might have been related to the exposures, we performed an analysis that included as events participants who reported a physician-diagnosed blockage in the arteries of the heart as well as all events in the main analysis.

In an exploratory analysis, we also considered the impact of short-term exposure to higher exposure levels by exploring risks associated with having exposures in the top 20th and 15th percentile of the single daily maximum exposure for a minimum of 7 or 14 d in comparison with having daily maximum exposures in the lowest quintile.

We used quantile g-computation (QGC)[56] to estimate the joint effect of BTEX-H as a mixture on the risk of CHD events. This method is a special case of g-computation, which is a generalization of standardization to continuous and time-varying confounders.[56] The method can be applied to any generalized linear model. We used the approach described in White et al.,[57] which implements QGC in the context of a Cox proportional hazards model. Under the assumption that the effects of each exposure are linear and additive (with respect to the log-hazard) on the quantile basis, Keil et al.[56] showed that QGC can be implemented using a standard Cox model with transformed exposures. In this analysis, we categorized exposure components into quintiles and assigned each quintile an integer score ($Q1 = 1, \ldots, Q5 = 5$). We then fit a Cox proportional hazards model of CHD against the quintile scores (treated as continuous variables), conditional on the same covariates used in single-agent IP-exposure weight models. This construction allows a weight for each BTEX-H component to represent a component's relative contribution to positive associations (positive weights), or relative contribution to inverse associations (negative weights). Positive and negative weights sum to 1 and −1, respectively. Under assumptions of linearity and additivity of the effects of BTEX-H, the joint effect equals the sum of generalized linear model coefficients for all of the transformed exposures, and it is interpreted as the expected change in the log-hazard of CHD for a simultaneous one quantile increase in all of the exposures in the BTEX-H mixture. As in single-agent analyses, we applied IP-censoring weights to the mixture model. Quantile g-computation was performed using R (version 4.0.4; R Development Core Team; package "qgcomp"). To facilitate comparison with the mixture model, we additionally performed single-pollutant analyses of each BTEX-H chemical modeled the same way as that in the QGC analysis (i.e., with integer scores assigned to each quintile) to assess changes in hazard of CHD per quintile increase in exposures.

All other analyses were performed using SAS (version 9.4; SAS Institute Inc.). An alpha level of 0.05 was considered statistically significant for all analyses.

Results

In comparison with the full analytical sample ($n = 22{,}655$), those who completed the first ($n = 15{,}627$) or second ($n = 10{,}638$) follow-up interviews tended to be older, female, White, and former or never smokers (Table 1). They were also more likely to have graduated from a 4-y college and to reside outside the Gulf states. There was no substantive difference in the other characteristics. Workers in the full analytical sample were exposed to crude oil for a median 4 months (range: 1 d–15 months).

During a median follow-up of 58 months (range: 1–116 months) beginning after each worker's last date of cleanup work, 509 out of 22,655 workers experienced an incident CHD event. This group of 509 workers included 428 cases of nonfatal MI, 7 cases of nonfatal MI with a later fatal CHD event, and 74 fatal CHD events without a history of reported MI. Over 90% of cases ($n = 451$) occurred among participants who were age 40 y or older at enrollment (Table S2). Almost 60% of the cases ($n = 304$) occurred within 4 y of follow-up, and 21.6% of cases ($n = 110$) were among participants followed for more than 6 y after exposure (Table S2). Among all workers in the study, half of the participants were exposed to crude oil chemicals from OSRC for ≥4 months (Table 2).

In the IP-censoring weighted analysis, we saw modest increases in risk of CHD among those in the higher quintiles of cumulative daily maximum exposure to each agent in comparison with workers in the referent group. All exposure agents showed the strongest association in the top quintile (range of HR = 1.19–1.44), with the highest and significant HRs observed for THC (HR = 1.42; 95% CI: 1.01, 2.01) and benzene (HR = 1.44; 95% CI: 1.02, 2.02) (Table 3). Only THC showed elevated risks across all quintiles above the reference quintile. There were no apparent exposure–response trends for any exposure agents, and tests of trend were nonsignificant. Similar patterns of association were seen for cumulative daily average exposures (Table 3). The mean and range of the stabilized IP weights for each cumulative exposure are shown in

Table 1. Characteristics of *DWH* disaster oil spill workers who responded to the enrollment, first follow-up, and second follow-up interviews, respectively.

Characteristic	Enrollment[a] ($n = 22,655$) *n* (%)	1st follow-up[b] ($n = 15,627$) *n* (%)	2nd follow-up[c] ($n = 10,638$) *n* (%)
Age at enrollment (y)			
20–29	4,803 (21.2)	2,822 (18.1)	1,782 (16.8)
30–39	5,586 (24.7)	3,567 (22.8)	2,304 (21.7)
40–49	5,585 (24.7)	3,973 (25.4)	2,708 (25.5)
50–59	4,762 (21.0)	3,703 (23.7)	2,666 (25.1)
≥60	1,919 (8.5)	1,562 (10.0)	1,178 (11.1)
Sex			
Male	18,627 (82.2)	12,736 (81.5)	8,548 (80.4)
Female	4,028 (17.8)	2,891 (18.5)	2,090 (19.7)
Race			
White	15,066 (66.5)	10,550 (67.5)	7,649 (71.9)
Black	5,303 (23.4)	3,550 (22.7)	2,043 (19.2)
Asian	202 (0.9)	120 (0.8)	78 (0.7)
American Indian or Alaskan Native	400 (1.8)	287 (1.8)	180 (1.7)
Native Hawaiian or Pacific Islander	47 (0.2)	31 (0.2)	22 (0.2)
Other race	1,033 (4.6)	654 (4.2)	391 (3.7)
Multiracial	604 (2.7)	435 (2.8)	275 (2.6)
Hispanic ethnicity			
No	21,141 (93.3)	14,632 (93.6)	10,023 (94.2)
Yes	1,514 (6.7)	995 (6.4)	615 (5.8)
Educational attainment			
Less than high school	3,470 (15.3)	2,210 (14.1)	1,207 (11.4)
High school diploma/GED	6,697 (29.6)	4,358 (27.9)	2,697 (25.4)
Some college/2-y degree	6,851 (30.2)	4,719 (30.2)	3,238 (30.4)
4-y college graduate or more	5,637 (24.9)	4,340 (27.8)	3,496 (32.9)
Weight classification			
Underweight or normal (BMI <25)	6,146 (27.1)	4,131 (26.4)	2,746 (25.8)
Overweight (25 ≤ BMI <30)	9,419 (41.6)	6,516 (41.7)	4,534 (42.6)
Obese I (30 ≤ BMI <35)	4,633 (20.5)	3,234 (20.7)	2,198 (20.7)
Obese II (BMI ≥35)	2,457 (10.9)	1,746 (11.2)	1,160 (10.9)
Reported precleanup diabetes diagnosis			
No	21,621 (95.4)	14,851 (95.0)	10,124 (95.2)
Yes	1,034 (4.6)	776 (5.0)	514 (4.8)
Reported prespill hypertension diagnosis			
No	18,245 (81.9)	12,365 (80.5)	8,373 (80.0)
Yes	4,034 (18.1)	2,992 (19.5)	2,092 (20.0)
Missing	376	270	173
Smoking status			
Current heavy smoker (≥20 cigarettes/day)	2,266 (10.0)	1,455 (9.3)	845 (7.9)
Current light smoker (<20 cigarettes/day)	4,524 (20.0)	2,883 (18.5)	1,717 (16.1)
Former smoker	4,783 (21.1)	3,431 (22.0)	2,467 (23.2)
Never smoked	11,082 (48.9)	7,858 (50.3)	5,609 (52.7)
Residential county proximity to Gulf of Mexico[d]			
Direct or indirect contact	13,339 (58.9)	8,946 (57.3)	5,733 (53.9)
Other Gulf state residence	4,639 (20.5)	3,138 (20.1)	2,153 (20.2)
Non–Gulf state residence	4,677 (20.6)	3,543 (22.7)	2,752 (25.9)
Previous oil spill cleanup work			
No	19,809 (87.4)	13,524 (86.5)	9,110 (85.6)
Yes	2,846 (12.6)	2,103 (13.5)	1,528 (14.4)
Previous oil industry experience			
No	19,113 (84.4)	13,108 (83.9)	8,971 (84.3)
Yes	3,542 (15.6)	2,519 (16.1)	1,667 (15.7)
Ever had to stop working because of heat			
No	13,383 (65.7)	9,271 (66.4)	6,443 (68.6)
Yes	6,980 (34.3)	4,693 (33.6)	2,943 (31.4)
Missing	2,292	1,663	1,252
Worked any job involving oily wildlife, oily plants, or dead animal recovery			
No	16,287 (72.9)	11,315 (73.5)	8,018 (76.4)
Yes	6,049 (27.1)	4,077 (26.5)	2,474 (23.6)
Missing	319	235	146

Note: All characteristics were self-reported or derived from information that was self-reported at enrollment. BMI, body mass index; *DWH*, *Deepwater Horizon*; GED, general equivalency diploma.

[a]Enrollment interview occurred from March 2011 to May 2013.

[b]First follow-up interview occurred from May 2013 to April 2016.

[c]Second follow-up interview occurred from November 2017 to July 2021.

[d]Direct proximity is defined as living in a county directly adjacent to the Gulf of Mexico; indirect is defined as living in a county adjacent to coastal counties.

Table 2. Distribution (range and quintiles) of duration of exposure, cumulative daily maximum exposure, cumulative daily average exposure, and single daily maximum exposure to crude oil chemicals among *DWH* disaster oil spill workers ($n = 22{,}655$), 2010–2019.

	Minimum	Q1 cut point	Q2 cut point	Median	Q3 cut point	Q4 cut point	Maximum
Duration of exposure (months)	>0	2	3	4	5	8	15
Cumulative daily maximum							
THC (ppm-day)	0.01	7.1	30.6	49.9	75.2	167.2	1,243.8
Benzene (ppb-day)	0.01	34.4	187.9	312.1	494.2	1,195.8	10,591.7
Toluene (ppb-day)	0.12	119.8	758.2	1,264.5	1,991.7	4,399.1	29,656.6
Ethylbenzene (ppb-day)	0.01	29.8	152.8	246.8	380.7	933.8	8,129.9
Xylene (ppb-day)	1.58	523.9	1,240.4	1,710.2	2,449.9	4,917.0	24,935.7
n-Hexane (ppb-day)	0.06	55.3	310.1	522.2	959.4	3,333.0	90,157.5
Cumulative daily average							
THC (ppm-day)	0.01	5.5	19.4	30.5	44.9	86.9	761.2
Benzene (ppb-day)	0.01	23.1	115.9	182.6	270.1	598.8	7,744.1
Toluene (ppb-day)	0.12	85.4	439.5	717.7	1,092.5	2,219.2	18,067.9
Ethylbenzene (ppb-day)	0.01	19.2	99.2	151.1	217.6	455.9	8,082.1
Xylene (ppb-day)	1.58	430.5	909.0	1,234.0	1,612.5	2,770.0	24,413.1
n-Hexane (ppb-day)	0.06	39.4	181.3	290.3	504.7	1,507.7	62,717.1
Single daily maximum							
THC (ppm)	0.01	0.2	0.6	0.4	1.2	2.8	22.4
Benzene (ppb)	0.00	1.3	3.1	1.9	8.9	15.1	62.5
Toluene (ppb)	0.04	4.6	16.2	7.0	38.3	66.9	188.0
Ethylbenzene (ppb)	0.00	1.2	2.4	1.4	6.2	16.0	137.0
Xylene (ppb)	0.51	10.2	17.1	11.9	39.8	75.0	445.3
n-Hexane (ppb)	0.06	2.2	6.0	3.6	25.3	68.1	2,441.0

Note: *DWH*, *Deepwater Horizon*; ppb, parts per billion; ppm, parts per million; Q, quintile; THC, total hydrocarbons.

Table S3. We observed similar results in analyses without IP-censoring weights (Table S4).

Among ever smokers, we observed increased risk of CHD in the top quintile of cumulative daily maximum exposure to all agents, including statistically significant increases for THC (HR = 1.92; 95% CI: 1.25, 2.97) and benzene (HR = 1.52; 95% CI: 1.00, 2.33) (Table 4). Among never smokers, we found elevated HRs in the top quintile of cumulative daily maximum exposure to benzene, xylene, and *n*-hexane, although none of the associations were statistically significant. Results were generally similar when we evaluated cumulative daily average exposures, although associations among never smokers were more attenuated (Table S5). When we stratified analyses by education, associations for all agents were more pronounced among workers with high school education or less than among those with more than high school education (Table 5; Table S6). In analyses stratified by BMI, we observed stronger associations among workers who were nonobese in comparison with those who were obese (Table 6; Table S7). When we restricted the analysis to participants who were age 40 y or older, we observed generally similar associations, although risk estimates in the second and third quintiles of exposure to some agents became slightly stronger (Table S8).

We observed similar results in sensitivity analyses in which we, separately, accounted for precleanup hypertension (Tables S9), modeled age as splines (Table S10), included fatal events with CHD as a contributing/underlying cause of death (Table S11), or limited the outcome to nonfatal MI (Table S12). Results were also similar when we began follow-up at the time of enrollment instead of after each worker's last date of cleanup work (Table S13). The analysis that excluded workers who had higher $PM_{2.5}$ exposure from controlled burning produced somewhat attenuated effect estimates, especially in the top quintile, but results were not substantively different (Table S14). When we accounted in the model for ever having to stop working during the cleanup because of heat, we observed stronger associations for several exposure agents (Table S15). There was no substantive difference in results when we accounted for workers performing jobs that involved handling oily plants/wildlife or dead animal recovery (Table S16). In comparison with previously published results from this cohort, we observed elevated HRs in all upper quintiles of single daily maximum THC exposure in relation to CHD events accrued until the first follow-up interview and similar risk estimates when follow-up was extended to December 2019 (Table S17). When we coarsened the time interval in which CHD events were identified to explore the potential impact of in accurately recalling the date of CHD diagnosis (by up to a few months), we observed minimal difference in associations (Table S18). In the sensitivity analysis where we also included as cases workers who reported being diagnosed with a blockage in the arteries of the heart, we observed somewhat attenuated associations (Table S19).

In the subanalysis exploring risk of CHD among workers who had higher daily exposures for varying numbers of days, we observed nonsignificantly elevated HRs in comparison with workers who had consistently lower daily exposures (Table S20). As we increased the thresholds for daily exposure level from top 20th to top 15th percentile of single daily maximum exposure and for exposure duration from ≥7 to ≥14 d, we observed stronger effects for toluene but no noticeable changes in association for the other agents.

When we assessed the joint effect of the BTEX-H mixture using quantile g-computation, we found a negligible association for a per quintile increase in the entire mixture on CHD incidence (Table 7). A one quintile increase in cumulative daily maximum exposure and cumulative daily average exposure to all chemicals was associated with an increased risk of CHD of 1.03 (95% CI: 0.96, 1.10) and 1.02 (95% CI: 0.95, 1.09), respectively. Single-agent models that examined per quintile increase in exposures showed effect estimates of similar magnitude (Table 3).

Discussion

In this study, we examined the relationship between exposure to THC and BTEX-H and risk of CHD among oil spill workers up to 10 y after the *DWH* disaster. We observed a modest increase in risk of CHD among workers in the top quintile of cumulative exposure to these agents. Although there was no clear evidence of exposure–response trends and effect estimates in the upper quintiles of most exposure agents were not statistically significant, the magnitude of the effect in the highest exposure quintile in the main analysis was clinically meaningful and comparable

Table 3. Associations between cumulative exposure to crude oil chemicals and incident CHD events among *DWH* disaster oil spill workers ($n = 22,655$), 2010–2019.

	Cumulative daily maximum			Cumulative daily average		
Exposure	Total cases ($n = 509$)	Total no. ($n = 22,655$)	HR (95% CI)[a]	Total cases ($n = 509$)	Total no. ($n = 22,655$)	HR (95% CI)[a]
THC (ppm-days[b])						
Q1	75	4,531	Ref	88	4,533	Ref
Q2	111	4,531	1.29 (0.92, 1.80)	106	4,529	1.08 (0.79, 1.47)
Q3	105	4,531	1.19 (0.85, 1.66)	97	4,531	0.92 (0.67, 1.26)
Q4	102	4,531	1.18 (0.84, 1.66)	104	4,531	1.00 (0.73, 1.36)
Q5	116	4,531	1.42 (1.01, 2.01)	114	4,531	1.21 (0.88, 1.66)
Per ln(ppm-day) increase[c]	—	—	1.05 (1.00, 1.10)	—	—	1.05 (0.99, 1.11)
Benzene (ppb-days[b])						
Q1	73	4,531	Ref	74	4,533	Ref
Q2	113	4,531	1.29 (0.92, 1.82)	112	4,529	1.35 (0.96, 1.91)
Q3	113	4,531	1.30 (0.92, 1.83)	116	4,531	1.31 (0.93, 1.83)
Q4	81	4,531	0.89 (0.62, 1.28)	81	4,531	0.91 (0.64, 1.30)
Q5	129	4,531	1.44 (1.02, 2.02)	126	4,531	1.39 (0.99, 1.97)
Per ln(ppb-day) increase[c]	—	—	1.04 (1.00, 1.09)	—	—	1.03 (0.99, 1.08)
Per quintile increase[d]	—	—	1.03 (0.96, 1.10)	—	—	1.02 (0.95, 1.09)
Toluene (ppb-days[b])						
Q1	80	4,531	Ref	84	4,531	Ref
Q2	109	4,531	1.19 (0.86, 1.66)	106	4,531	1.10 (0.79, 1.53)
Q3	99	4,531	1.01 (0.72, 1.42)	105	4,531	1.04 (0.75, 1.44)
Q4	92	4,531	0.90 (0.64, 1.27)	83	4,531	0.79 (0.56, 1.11)
Q5	129	4,531	1.26 (0.91, 1.74)	131	4,531	1.26 (0.90, 1.77)
Per ln(ppb-day) increase[c]	—	—	1.04 (0.99, 1.09)	—	—	1.03 (0.98, 1.08)
Per quintile increase[d]	—	—	1.01 (0.95, 1.09)	—	—	1.02 (0.95, 1.10)
Ethylbenzene (ppb-days[b])						
Q1	83	4,531	Ref	82	4,531	Ref
Q2	104	4,531	1.02 (0.73, 1.43)	103	4,531	1.09 (0.79, 1.52)
Q3	114	4,531	1.10 (0.79, 1.52)	116	4,531	1.15 (0.84, 1.59)
Q4	93	4,531	0.87 (0.62, 1.21)	95	4,531	0.95 (0.68, 1.33)
Q5	115	4,531	1.19 (0.85, 1.66)	113	4,531	1.22 (0.87, 1.71)
Per ln(ppb-day) increase[c]	—	—	1.04 (0.99, 1.08)	—	—	1.04 (0.99, 1.09)
Per quintile increase[d]	—	—	1.01 (0.94, 1.08)	—	—	1.01 (0.95, 1.09)
Xylene (ppb-days[b])						
Q1	87	4,533	Ref	99	4,531	Ref
Q2	104	4,529	1.12 (0.82, 1.52)	97	4,531	0.90 (0.67, 1.22)
Q3	110	4,531	1.16 (0.85, 1.57)	97	4,534	0.91 (0.68, 1.22)
Q4	90	4,531	0.87 (0.64, 1.19)	94	4,528	0.81 (0.61, 1.10)
Q5	118	4,531	1.25 (0.91, 1.70)	122	4,531	1.14 (0.85, 1.53)
Per ln(ppb-day) increase[c]	—	—	1.04 (0.97, 1.11)	—	—	1.03 (0.95, 1.11)
Per quintile increase[d]	—	—	1.02 (0.95, 1.09)	—	—	1.01 (0.95, 1.09)
n-Hexane (ppb-days[b])						
Q1	75	4,531	Ref	76	4,577	Ref
Q2	100	4,531	1.10 (0.77, 1.56)	108	4,485	1.19 (0.84, 1.67)
Q3	115	4,531	1.24 (0.88, 1.74)	101	4,531	1.06 (0.75, 1.50)
Q4	102	4,531	1.00 (0.71, 1.42)	106	4,531	1.03 (0.73, 1.46)
Q5	117	4,531	1.34 (0.94, 1.91)	118	4,531	1.31 (0.92, 1.86)
Per ln(ppb-day) increase[c]	—	—	1.04 (1.00, 1.08)	—	—	1.03 (0.99, 1.08)
Per quintile increase[d]	—	—	1.04 (0.97, 1.12)	—	—	1.04 (0.97, 1.11)

Note: Incident CHD events defined as either a self-reported physician-diagnosed myocardial infarction or an *International Classification of Diseases*-coded fatal CHD event that occurred after the last day of participants' oil spill cleanup work. —, no data; CHD, coronary heart disease; CI, confidence interval; *DWH*, *Deepwater Horizon*; HR, hazard ratio; ppb, parts per billion; ppm, parts per million; Ref, reference; THC, total hydrocarbons.

[a]Inverse probability exposure-weighted Cox proportional hazards models accounted for age, sex, race, ethnicity, weight class, smoking, precleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience. Covariates were coded as shown in Table 1, except for race, which was coded as White, Black, and other/multiracial groups.

[b]See Table 2 for the range (minimum, maximum) of exposure values corresponding to each exposure quintile.

[c]Exposure–response analyses of ln-transformed continuous cumulative exposures (in units of ppm-days for THC and ppb-days for all other exposure agents). Exposures were ln-transformed to reduce skewness.

[d]Analysis performed only for comparison with the quantile g-computation model on BTEX-H (benzene, toluene, ethylbenzene, xylene, *n*-hexane) mixture. Each exposure quintile was assigned an integer score (Q1 = 1, Q2 = 2, Q3 = 3, Q4 = 4, and Q5 = 5).

to the increase in CHD risk from secondhand smoke exposure among nonsmokers (relative risk: 1.3), as estimated in a meta-analysis.[58] In subgroup analyses, effect estimates were more pronounced among ever smokers, workers who had high school education or less, and workers who were not obese. In these subgroups, effect estimates in the top quintile of exposure to some agents were approaching the increase in risk of CHD comparing individuals who smoked one cigarette per day to never smokers (relative risk: 1.48–1.57), as reported in a recent, large meta-analysis.[59]

Several epidemiological studies have assessed ambient levels of volatile hydrocarbons in relation to MI and CHD events.[8,9,60] Unlike these air pollution studies, which assessed exposure either across several days or over a year, most workers in our study were exposed to BTEX-H for several months. The maximum exposure levels experienced by workers in our study were generally higher than those reported in these air pollution studies but were well below occupational guidelines set by the American Conference of Governmental Industrial Hygienists (Table 2).[61] Differences in exposure duration, emission source, and length of follow-up limits a

Table 4. Modification of the associations between cumulative daily maximum exposure to crude oil chemicals and incident CHD events by smoking status among *DWH* disaster oil spill workers ($n = 22{,}655$), 2010–2019.

	Ever smokers			Never smokers			
Exposure	Total cases ($n = 337$)	Total no. ($n = 11{,}573$)	HR (95% CI)[a]	Total cases ($n = 172$)	Total no. ($n = 11{,}082$)	HR (95% CI)[a]	p for interaction[d]
THC (ppm-days[b])							
Q1	40	1,850	Ref	35	2,681	Ref	0.10
Q2	78	2,307	1.81 (1.19, 2.76)	33	2,224	0.74 (0.42, 1.28)	—
Q3	71	2,392	1.55 (1.02, 2.37)	34	2,139	0.82 (0.48, 1.42)	—
Q4	68	2,472	1.50 (0.98, 2.30)	34	2,059	0.88 (0.51, 1.52)	—
Q5	80	2,552	1.92 (1.25, 2.97)	36	1,979	0.88 (0.51, 1.53)	—
Per ln(ppm-day) increase[c]	—	—	1.05 (0.99, 1.13)	—	—	1.05 (0.97, 1.13)	—
Benzene (ppb-days[b])							
Q1	42	1,806	Ref	31	2,725	Ref	0.86
Q2	73	2,345	1.34 (0.87, 2.06)	40	2,186	1.27 (0.74, 2.19)	—
Q3	79	2,335	1.47 (0.96, 2.24)	34	2,196	1.06 (0.61, 1.86)	—
Q4	56	2,462	0.93 (0.60, 1.46)	25	2,069	0.88 (0.48, 1.61)	—
Q5	87	2,625	1.52 (1.00, 2.33)	42	1,906	1.34 (0.77, 2.32)	—
Per ln(ppb-day) increase[c]	—	—	1.04 (0.98, 1.09)	—	—	1.05 (0.98, 1.13)	—
Toluene (ppb-days[b])							
Q1	48	1,823	Ref	32	2,708	Ref	0.63
Q2	69	2,288	1.17 (0.77, 1.78)	40	2,243	1.27 (0.74, 2.18)	—
Q3	70	2,326	1.11 (0.73, 1.67)	29	2,205	0.89 (0.51, 1.58)	—
Q4	58	2,516	0.87 (0.56, 1.33)	34	2,015	1.02 (0.59, 1.79)	—
Q5	92	2,620	1.37 (0.92, 2.05)	37	1,911	1.09 (0.63, 1.91)	—
Per ln(ppb-day) increase[c]	—	—	1.05 (0.98, 1.11)	—	—	1.05 (0.98, 1.13)	—
Ethylbenzene (ppb-days[b])							
Q1	49	1,820	Ref	34	2,711	Ref	0.53
Q2	71	2,337	1.07 (0.71, 1.62)	33	2,194	0.95 (0.55, 1.64)	—
Q3	71	2,369	1.01 (0.67, 1.52)	43	2,162	1.32 (0.79, 2.22)	—
Q4	65	2,447	0.94 (0.62, 1.43)	28	2,084	0.78 (0.44, 1.39)	—
Q5	81	2,600	1.24 (0.82, 1.89)	34	1,931	1.11 (0.64, 1.92)	—
Per ln(ppb-day) increase[c]	—	—	1.04 (0.98, 1.10)	—	—	1.03 (0.97, 1.11)	—
Xylene (ppb-days[b])							
Q1	55	1,988	Ref	32	2,545	Ref	0.81
Q2	67	2,207	1.15 (0.78, 1.68)	37	2,322	1.22 (0.73, 2.04)	—
Q3	68	2,305	1.07 (0.74, 1.57)	42	2,226	1.43 (0.86, 2.36)	—
Q4	63	2,477	0.91 (0.62, 1.34)	27	2,054	0.87 (0.50, 1.52)	—
Q5	84	2,596	1.30 (0.89, 1.89)	34	1,935	1.22 (0.71, 2.07)	—
Per ln(ppb-day) increase[c]	—	—	1.05 (0.96, 1.15)	—	—	1.05 (0.94, 1.18)	—
n-Hexane (ppb-days[b])							
Q1	43	1,816	Ref	32	2,715	Ref	0.98
Q2	63	2,281	1.11 (0.71, 1.73)	37	2,250	1.11 (0.64, 1.93)	—
Q3	78	2,426	1.31 (0.85, 2.01)	37	2,105	1.15 (0.66, 2.00)	—
Q4	71	2,488	1.12 (0.73, 1.73)	31	2,043	0.87 (0.49, 1.56)	—
Q5	82	2,562	1.46 (0.94, 2.27)	35	1,969	1.20 (0.68, 2.12)	—
Per ln(ppb-day) increase[c]	—	—	1.06 (1.00, 1.12)	—	—	1.02 (0.96, 1.08)	—

Note: Incident CHD events defined as either a self-reported physician-diagnosed myocardial infarction or an *International Classification of Diseases*-coded fatal CHD event that occurred after the last day of participants' oil spill cleanup work. —, no data; CHD, coronary heart disease; CI, confidence interval; *DWH*, *Deepwater Horizon*; HR, hazard ratio; ppb, parts per billion; ppm, parts per million; Ref, reference; THC, total hydrocarbons.

[a]Inverse probability exposure-weighted Cox proportional hazards models accounted for age, sex, race, ethnicity, weight class, smoking, precleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience. Covariates were coded as shown in Table 1, except for race, which was coded as White, Black, and other/multiracial groups.

[b]See Table 2 for the range (minimum, maximum) of exposure values corresponding to each exposure quintile.

[c]Exposure–response analyses of ln-transformed continuous cumulative exposures (in units of ppm-days for THC and ppb-days for all other exposure agents). Exposures were ln-transformed to reduce skewness.

[d]p-Value for joint Wald test that assessed effect measure modification of the associations between crude oil exposures and hazard of CHD by smoking.

direct comparison of our effect estimates with those of the other studies.

Among studies that focused on a longer exposure window, Barceló et al.[9] reported higher risk of MI mortality for an increase in annual average daily levels of benzene, which is consistent with our results. Our analyses addressed limitations in this prior study by accounting for covariates such as education and smoking. Moreover, the longer follow-up time in our study allowed us to observe the sustained effect many years after exposure. Self-reported MI was also associated with annual mean concentrations of benzene among residents in an industrial area of Estonia, but interpretation of the findings was limited by the cross-sectional study design.[62]

Studies that focused on short-term exposures have also shown modest acute effects on cardiovascular health, including positive associations of benzene exposure across several days with MI occurrence[6] and emergency hospitalizations for heart failure,[60] and of benzene and alkylbenzene concentrations with circulatory mortality.[7,8] These latter two studies have also associated acute cardiovascular events with exposure to alkanes,[8,60] but we are unaware of any study that examined the alkane *n*-hexane specifically. In our analysis, we were underpowered to examine acute effects of exposure because only 22 (nonfatal) MI events occurred within a month of the individuals' last day of cleanup work, and we lacked data on preenrollment fatal CHD events. Overall, however, the results of our study add to existing evidence that exposure to BTEX-H is associated with a modest increase in risk of CHD even at levels below the occupational limits, with a potential for persistent effects years after exposure.

Table 5. Modification of the associations between cumulative daily maximum exposure to crude oil chemicals and incident CHD events by highest education attained among *DWH* disaster oil spill workers ($n = 22,655$), 2010–2019.

	High school or less			More than high school			
Exposure	Total cases ($n = 293$)	Total no. ($n = 10,167$)	HR (95% CI)[a]	Total cases ($n = 216$)	Total no. ($n = 12,488$)	HR (95% CI)[a]	p for interaction[d]
THC (ppm-days[b])							
Q1	25	1,186	Ref	50	3,345	Ref	0.16
Q2	63	2,044	1.62 (0.98, 2.68)	48	2,487	0.97 (0.62, 1.53)	—
Q3	61	2,167	1.50 (0.91, 2.48)	44	2,364	0.90 (0.57, 1.42)	—
Q4	74	2,298	1.73 (1.06, 2.82)	28	2,233	0.66 (0.40, 1.10)	—
Q5	70	2,472	1.72 (1.04, 2.84)	46	2,059	1.15 (0.71, 1.88)	—
Per ln(ppm-day) increase[c]	—	—	1.07 (0.99, 1.16)	—	—	1.00 (0.93, 1.08)	—
Benzene (ppb-days[b])							
Q1	24	1,093	Ref	49	3,438	Ref	0.64
Q2	67	2,104	1.61 (0.98, 2.66)	46	2,427	1.00 (0.63, 1.59)	—
Q3	65	2,124	1.55 (0.94, 2.56)	48	2,407	1.04 (0.66, 1.64)	—
Q4	49	2,283	1.01 (0.60, 1.70)	32	2,248	0.75 (0.45, 1.25)	—
Q5	88	2,563	1.84 (1.13, 3.01)	41	1,968	1.02 (0.63, 1.65)	—
Per ln(ppb-day) increase[c]	—	—	1.07 (1.00, 1.15)	—	—	1.01 (0.95, 1.07)	—
Toluene (ppb-days[b])							
Q1	26	1,112	Ref	54	3,419	Ref	0.15
Q2	70	2,039	1.59 (0.97, 2.60)	39	2,492	0.79 (0.49, 1.25)	—
Q3	50	2,077	1.02 (0.61, 1.71)	49	2,454	0.94 (0.61, 1.46)	—
Q4	62	2,386	1.05 (0.64, 1.73)	30	2,145	0.71 (0.43, 1.17)	—
Q5	85	2,553	1.54 (0.95, 2.50)	44	1,978	0.91 (0.58, 1.44)	—
Per ln(ppb-day) increase[c]	—	—	1.07 (0.99, 1.15)	—	—	1.01 (0.94, 1.07)	—
Ethylbenzene (ppb-days[b])							
Q1	27	1,115	Ref	56	3,416	Ref	0.05
Q2	68	2,090	1.51 (0.93, 2.45)	36	2,441	0.62 (0.39, 0.99)	—
Q3	61	2,166	1.25 (0.77, 2.04)	53	2,365	0.98 (0.64, 1.49)	—
Q4	58	2,426	1.02 (0.62, 1.66)	35	2,105	0.72 (0.45, 1.15)	—
Q5	79	2,370	1.67 (1.03, 2.71)	36	2,161	0.79 (0.48, 1.32)	—
Per ln(ppb-day) increase[c]	—	—	1.05 (0.98, 1.13)	—	—	1.01 (0.95, 1.07)	—
Xylene (ppb-days[b])							
Q1	35	1,499	Ref	52	3,034	Ref	0.25
Q2	62	1,868	1.54 (1.00, 2.38)	42	2,661	0.78 (0.50, 1.22)	—
Q3	58	1,989	1.44 (0.93, 2.22)	52	2,542	0.93 (0.61, 1.42)	—
Q4	63	2,375	1.21 (0.79, 1.85)	27	2,156	0.54 (0.33, 0.89)	—
Q5	75	2,436	1.57 (1.02, 2.40)	43	2,095	1.00 (0.62, 1.61)	—
Per ln(ppb-day) increase[c]	—	—	1.09 (0.98, 1.21)	—	—	0.98 (0.88, 1.09)	—
n-Hexane (ppb-days[b])							
Q1	27	1,080	Ref	48	3,451	Ref	0.17
Q2	64	2,152	1.26 (0.77, 2.06)	36	2,379	0.90 (0.55, 1.46)	—
Q3	57	2,203	1.11 (0.67, 1.83)	58	2,328	1.36 (0.88, 2.11)	—
Q4	67	2,275	1.14 (0.70, 1.85)	35	2,256	0.80 (0.49, 1.30)	—
Q5	78	2,457	1.50 (0.92, 2.45)	39	2,074	1.16 (0.69, 1.93)	—
Per ln(ppb-day) increase[c]	—	—	1.04 (0.98, 1.10)	—	—	1.01 (0.95, 1.08)	—

Note: Incident CHD events defined as either a self-reported physician-diagnosed myocardial infarction or an *International Classification of Disease*-coded fatal CHD event that occurred after the last day of participants' oil spill cleanup work. —, no data; CHD, coronary heart disease; CI, confidence interval; *DWH*, *Deepwater Horizon*; HR, hazard ratio; ppb, parts per billion; ppm, parts per million; Ref, reference; THC, total hydrocarbons.

[a]Inverse probability exposure-weighted Cox proportional hazards models accounted for age, sex, race, ethnicity, weight class, smoking, precleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience. Covariates were coded as shown in Table 1, except for race, which was coded as White, Black, and other/multiracial groups.

[b]See Table 2 for the range (minimum, maximum) of exposure values corresponding to each exposure quintile.

[c]Exposure–response analyses of ln-transformed continuous cumulative exposures (in units of ppm-days for THC and ppb-days for all other exposure agents). Exposures were ln-transformed to reduce skewness.

[d]p-Value for joint Wald test that assessed effect measure modification of the associations between crude oil exposures and hazard of CHD by education.

As closely related volatile components of the crude oil, BTEX-H are present in gasolines and used as solvents and industrial raw materials for manufacturing of consumer products.[63–67] All of these hydrocarbons have been detected at varying levels in vehicular exhaust, near sites of oil/gas operations and gas stations, and in certain occupational settings.[20,68–72] Because individuals are typically exposed to many or all of these chemicals simultaneously, estimating the overall mixture effect can help inform interventions that target the emission sources. To our knowledge, only one study has examined the joint effect of specific crude oil chemical groups in relation to acute cardiovascular events. Ye et al.[73] investigated emergency department visits for cardiovascular diseases and same-day exposure to prespecified chemical groups and found significant associations for most hydrocarbon groups although not for the aromatic group (which contains BTEX). In our mixture analysis, we also found little evidence of a joint effect for BTEX-H. In comparison with single-agent models that examined per quintile increase in each exposure, effects in the mixture model were not noticeably stronger. The overall weak associations in the mixture analysis and its single-agent counterparts could be attributed to the apparent nonlinear relationship between the exposure and the outcome, where effects were present only above an exposure threshold (e.g., in Q5). Because other ambient pollution studies only examined exposures continuously, it is unclear whether a threshold effect existed in those other studies.

To our knowledge, our study is the first to investigate quantitative BTEX-H exposures and risk of CHD in an occupational

Table 6. Modification of the associations between cumulative daily maximum exposure to crude oil chemicals and incident CHD events by obesity status among *DWH* disaster oil spill workers ($n = 22{,}655$), 2010–2019.

	Not obese (BMI <30)			Obese (BMI ≥30)			
Exposure	Total cases ($n = 305$)	Total no. ($n = 15{,}565$)	HR (95% CI)[a]	Total cases ($n = 204$)	Total no. ($n = 7{,}090$)	HR (95% CI)[a]	p for interaction[d]
THC (ppm-days[b])							
Q1	39	3,279	Ref	36	1,252	Ref	<0.01
Q2	69	3,125	1.95 (1.26, 3.02)	42	1,406	0.83 (0.50, 1.37)	—
Q3	70	3,077	1.88 (1.22, 2.91)	35	1,454	0.70 (0.42, 1.17)	—
Q4	50	3,048	1.41 (0.89, 2.24)	52	1,483	1.02 (0.63, 1.66)	—
Q5	77	3,036	2.27 (1.44, 3.56)	39	1,495	0.85 (0.51, 1.44)	—
Per ln(ppm-day) increase[c]	—	—	1.10 (1.03, 1.17)	—	—	1.00 (0.92, 1.08)	—
Benzene (ppb-days[b])							
Q1	38	3,274	Ref	35	1,257	Ref	0.06
Q2	64	3,082	1.59 (0.97, 2.61)	49	1,449	1.07 (0.65, 1.75)	—
Q3	72	3,107	1.79 (1.10, 2.90)	41	1,424	0.89 (0.54, 1.49)	—
Q4	57	3,113	1.36 (0.82, 2.24)	24	1,418	0.49 (0.28, 0.86)	—
Q5	74	2,989	1.79 (1.10, 2.92)	55	1,542	1.18 (0.72, 1.94)	—
Per ln(ppb-day) increase[c]	—	—	1.08 (1.03, 1.14)	—	—	0.99 (0.93, 1.06)	—
Toluene (ppb-days[b])							
Q1	46	3,285	Ref	34	1,246	Ref	0.51
Q2	64	3,107	1.40 (0.90, 2.17)	45	1,424	0.99 (0.60, 1.65)	—
Q3	58	3,099	1.17 (0.75, 1.82)	41	1,432	0.85 (0.51, 1.42)	—
Q4	58	3,044	1.16 (0.74, 1.82)	34	1,487	0.66 (0.39, 1.12)	—
Q5	79	3,030	1.51 (0.98, 2.32)	50	1,501	1.03 (0.62, 1.71)	—
Per ln(ppb-day) increase[c]	—	—	1.08 (1.02, 1.14)	—	—	1.00 (0.92, 1.07)	—
Ethylbenzene (ppb-days[b])							
Q1	44	3,280	Ref	39	1,251	Ref	0.36
Q2	65	3,121	1.34 (0.84, 2.14)	39	1,410	0.75 (0.46, 1.24)	—
Q3	69	3,045	1.41 (0.89, 2.24)	45	1,486	0.82 (0.50, 1.32)	—
Q4	57	3,035	1.17 (0.73, 1.87)	36	1,496	0.61 (0.37, 1.01)	—
Q5	70	3,084	1.52 (0.95, 2.45)	45	1,447	0.92 (0.56, 1.51)	—
Per ln(ppb-day) increase[c]	—	—	1.08 (1.02, 1.14)	—	—	0.99 (0.92, 1.06)	—
Xylene (ppb-days[b])							
Q1	51	3,259	Ref	36	1,274	Ref	0.99
Q2	64	3,130	1.20 (0.80, 1.80)	40	1,399	1.03 (0.64, 1.67)	—
Q3	66	3,092	1.21 (0.81, 1.81)	44	1,439	1.07 (0.67, 1.71)	—
Q4	54	3,008	0.96 (0.63, 1.45)	36	1,523	0.77 (0.47, 1.26)	—
Q5	70	3,076	1.30 (0.86, 1.98)	48	1,455	1.23 (0.77, 1.97)	—
Per ln(ppb-day) increase[c]	—	—	1.06 (0.97, 1.16)	—	—	1.01 (0.91, 1.13)	—
n-Hexane (ppb-days[b])							
Q1	42	3,282	Ref	33	1,249	Ref	0.82
Q2	60	3,050	1.25 (0.78, 2.02)	40	1,481	0.93 (0.55, 1.57)	—
Q3	71	3,110	1.45 (0.91, 2.31)	44	1,421	0.98 (0.59, 1.65)	—
Q4	61	3,084	1.16 (0.72, 1.87)	41	1,447	0.81 (0.48, 1.37)	—
Q5	71	3,039	1.56 (0.96, 2.52)	46	1,492	1.14 (0.67, 1.95)	—
Per ln(ppb-day) increase[c]	—	—	1.06 (1.01, 1.12)	—	—	1.01 (0.95, 1.08)	—

Note: Incident CHD events defined as either a self-reported physician-diagnosed myocardial infarction or an *International Classification of Diseases*-coded fatal CHD event that occurred after the last day of participants' oil spill cleanup work. —, no data; BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; *DWH*, *Deepwater Horizon*; HR, hazard ratio; ppb, parts per billion; ppm, parts per million; Ref, reference; THC, total hydrocarbons.

[a]Inverse probability exposure-weighted Cox proportional hazards models accounted for age, sex, race, ethnicity, weight class, smoking, precleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience. Covariates were coded as shown in Table 1, except for race, which was coded as White, Black, and other/multiracial groups.

[b]See Table 2 for the range (minimum, maximum) of exposure values corresponding to each exposure quintile.

[c]Exposure–response analyses of ln-transformed continuous cumulative exposures (in units of ppm-days for THC and ppb-days for all other exposure agents). Exposures were ln-transformed to reduce skewness.

[d]p-Value for joint Wald test that assessed effect measure modification of the associations between crude oil exposures and hazard of CHD by obesity.

setting. In an earlier analysis that followed the GuLF Study cohort for only 5 y, Strelitz et al.[17] found a statistically significant association between an ordinal measure of single daily maximum THC exposure and hazard of a CHD event. In addition, those who worked >180 d also had higher hazard of CHD in comparison with those who worked ≤30 d.[16] Longer duration of work was also associated with increased risks of self-reported MI or angina among *Hebei Spirit* oil spill workers up to 10 y after the spill.[14] Although studies have shown a positive relationship between duration of exposure and CHD risk, no study has assessed cumulative exposure to THC or specific chemicals, which accounts for exposure duration. Taking advantage of recently developed exposure estimates and a longer duration of follow-up, we showed that cumulative exposure to THC and BTEX-H was associated with increased risk of MI, although effect estimates were lower than that associated with the ordinal single daily maximum THC exposure observed previously. The stronger associations observed for the single daily maximum THC exposure suggest that exposure to crude oil chemicals at a high intensity might have induced damage, possibly inflammatory and/or vascular, that increased workers' risk of CHD over time. Workers with higher single daily maximum exposure, however, also tended to have higher cumulative exposures. In analyses that further assessed the role of exposure intensity in CHD risk by comparing workers who were exposed to higher daily maximum exposures for varying number of days with workers with consistently lower daily exposures, increasing the threshold of exposure intensity or exposure duration led to

Table 7. Quantile g-computation estimates for the change in CHD events hazards for a one quintile increase in cumulative exposure to all crude oil chemicals (BTEX-H) among *DWH* disaster oil spill workers ($n = 22{,}655$), 2010–2019.

	Cumulative daily maximum	Cumulative daily average
Exposure	HR (95% CI)[a]	HR (95% CI)[a]
Per quintile increase	1.03 (0.96, 1.10)	1.02 (0.95, 1.09)

Note: Incident CHD events were defined as either a self-reported physician-diagnosed myocardial infarction or an *International Classification of Disease*-coded fatal CHD event that occurred after the last day of participants' oil spill cleanup work. BTEX-H, volatile organic compound comprising benzene, toluene, ethylbenzene, xylene, *n*-hexane; CHD, coronary heart disease; CI, confidence interval; *DWH*, *Deepwater Horizon*; HR, hazard ratio.

[a]Quantile g-computation models accounted for age, sex, race, ethnicity, weight class, smoking, precleanup diabetes, education, residential proximity to the Gulf of Mexico, previous oil spill cleanup work, and previous oil industry experience. Covariates were coded as shown in Table 1, except for race, which was coded as White, Black, and other/multiracial groups.

stronger effect estimates for toluene, but no meaningful changes in associations were observed for the other exposure agents.

In analyses stratified by cigarette smoking status, we saw elevated risks in the top quintile of exposure to most agents in both ever and never smokers, although effects were generally more pronounced among ever smokers. In the analysis stratified by highest educational attainment, we found stronger effects in the subgroup with no more than high school education. This finding is consistent with two studies that found stronger associations between traffic-related air pollution and cardiovascular mortality among participants with lower educational attainment.[40,41]

In analyses stratified by obesity, we observed elevated HRs among workers with higher exposure to all agents in the non-obese subgroup, with generally weaker associations in the obese subgroup. One possible explanation for the weaker associations among the obese group is that variability of CHD risk is likely higher among these workers, so it is easy for the modest effect of oil exposures to be lost among this high variability. We hypothesize the risk to vary more among obese workers because their baseline risk was higher,[74] so lifestyle factors, such as physical activities, would have a larger impact to alter each individual's overall risk of CHD.[75] In addition, obese workers were more likely to have other cardiovascular comorbidities,[76] which would also have led to variability in CHD risk among this group. We were not able to account for all the lifestyle and health factors (e.g., diet, physical activity, cholesterol levels) that could have led to the wider range of risks in the obese group.

Two major mechanisms have been proposed that link short- and long-term exposure to air pollutants to CHD events. One mechanism involves activation of pulmonary and systemic inflammatory responses by inhaled pollutants.[77,78] This inflammation and associated oxidative stress can stimulate the circulatory release of inflammatory proteins and coagulation factors, accelerating atherosclerosis and increasing the potential for thrombosis. Although an individual's rate of atherosclerosis depends on their risk profile,[79] a recent study showed rapid atherosclerotic progression among participants 40–54 y of age and without a history of cardiovascular disease during 3 y of follow-up.[80] The vast majority of CHD cases in our study occurred among participants over 40 y old. Exposure to crude oil chemicals could have accelerated atherosclerosis among these workers and resulted in increased CHD events in the several years after exposure. The other mechanism involves modulation of the autonomic nervous system by pollutants trapped in the respiratory tract.[77,78] A shift of the system toward the sympathetic tone elevates blood pressure, which can lead to increased risk of CHD.[78] Among susceptible individuals with advanced atherosclerosis, air pollutant-induced inflammation and vasoconstriction may destabilize existing plaques and trigger an acute CHD event soon after exposure.[77,78] We lacked the necessary data and sufficient cases to examine the association between exposure to crude oil chemicals and acute CHD events in this study.

Evidence supporting these possible mechanisms comes from studies showing elevated levels of oxidative stress and inflammation[68,81–83] and higher risk of hypertension and electrocardiographic abnormalities[84–86] among workers exposed to BTEX-H chemicals. Higher levels of oxidative stress were also observed among *Hebei Spirit* oil spill responders in relation to work duration.[14] Among GuLF Study participants, cumulative THC exposure was associated with increased risk of hypertension 1–3 y after the spill.[87] In addition, Coast Guard responders who participated in the *DWH* spill cleanup and reported crude oil inhalation exposure had increased risks of essential hypertension and heart palpitations 3–5 y after the spill.[88] Together, current mechanistic understanding supports the plausibility of the observed cardiovascular effects of exposure to THC and BTEX-H.

A major strength of our study is the careful reconstruction of THC and BTEX-H exposures using personal air samples collected on the OSRC workers, as well as detailed work histories collected from the study participants. In addition, although most air pollution studies examined MI/CHD events immediately following either acute (days) or long-term (years) exposures, our study was unique in assessing medium-duration exposures that lasted weeks to a few months and persistent cardiovascular effects many years after cessation of exposure. Another strength of the study is the use of IP-censoring weights to account for potential informative censoring due to loss to follow-up. Associations were similar in the IP-weighted models and models without weights, suggesting that our results are robust to the potential bias from informative censoring. Last, subject-specific data on education, BMI, and smoking status allowed us to perform stratified analyses by these traits to identify groups that might be particularly vulnerable to the effects of these exposures. We are unaware of any studies of crude oil chemicals and CHD that have examined these effect measure modifiers.

One limitation of the study is potential misclassification of the outcome, as we could not obtain medical records from participants to confirm their MI diagnosis or cause of death. Previous studies have reported moderate to high accuracy of self-reported MI and of death certificate diagnosis of CHD, with sensitivities ranging from 0.78 to 0.98 and specificities varying from 0.72 to 1.0.[89–98] Many of these studies have associated lower accuracy with older age.[93,94,98,99] In comparison with participants examined in these validation studies, workers in our study were younger (most were <60 y of age at enrollment), so we expect a lower degree of outcome misclassification in our population. There could be measurement error in the reported event time due to participants' inaccurate recall of the date of MI diagnosis. However, exploratory analyses in which we coarsened the follow-up from 1 month to 4 months showed no notable changes from the main analysis results, which suggests that our analysis was robust to measurement error of at least a few months in recall time.

Second, the exposure estimates assigned to workers contain some degree of uncertainty.[18] The left-censored Bayesian method used to estimate EG average exposures had low bias and imprecision[25,26,100] and performed well for most EGs, but some EGs with extreme censoring or few measurements had more uncertainty.[21] However, this possibility is unlikely to have substantively biased our risk estimates in analyses using categorical exposures because the vast majority of workers in these generally low-exposure EGs fell into the lowest exposure category. In addition, although many participants worked on multiple jobs/tasks during the cleanup, we lack information on the specific days and the exact number of hours on those days that they

performed each job/activity, which increased uncertainty in the estimates of daily exposures. To overcome this limitation, we examined both cumulative daily maximum and cumulative daily average exposures, which produced similar results.

Third, in our analysis, we were not able to identify CHD deaths that occurred among OSRC workers between exposure and study enrollment because enrollment was contingent on survival. If more CHD deaths occurred before enrollment among *DWH* oil spill workers exposed to higher levels of crude oil chemicals, our results might have underestimated the true risk. However, given the relatively short time between exposure and enrollment (i.e., immortal time for the fatal outcome), the overall small number of fatal CHD cases during the entire follow-up, and the continued risk over the years of observation, we do not expect left truncation of these fatal events to meaningfully change our results. In a subanalysis, we examined nonfatal MI as the outcome, for which there was no immortal time bias, and observed similar associations. In another analysis, we explored the impact of starting follow-up at a worker's enrollment in the cohort rather than after the last day of their cleanup work and observed slightly attenuated associations.

Last, there could be bias from unmeasured confounders or imperfect measurement of existing covariates in the models, which may explain in part the lack of observed exposure–response trends. We lacked the necessary data to adjust for certain other potential exposures experienced during the oil spill cleanup.[4] In a sensitivity analysis, we accounted for one important occupational exposure that has been associated with CHD—$PM_{2.5}$ from controlled burning by excluding workers who experienced higher $PM_{2.5}$ exposure—and found somewhat attenuated results. The majority of workers who had higher $PM_{2.5}$ exposure were also exposed to higher levels of THC and BTEX-H (proportion in Q4 or Q5: 71%–91% by exposure agent). It is likely that workers who were exposed to both higher burning-related $PM_{2.5}$ and crude oil chemicals had even higher risks of CHD, but we had few cases to examine associations among this subgroup or to adjust for $PM_{2.5}$ exposure levels. We also accounted for a measure of heat stress and one OSRC work that could have induced psychological stress among workers and observed similar or stronger associations. There could also be a bias if workers were assigned to different jobs/activities based on their health factors at the time of spill that were predictive of their future CHD risk. We adjusted for several indicators of baseline health (BMI, precleanup diabetes, precleanup hypertension, smoking) to reduce this potential bias. Last, some of our adjustment factors, such as cigarette smoking and BMI, were ascertained at enrollment as proxies for factors at the time of exposure and might have changed over time. However, we expect little change in these factors over the short span between exposure and time of their ascertainment.

Our study showed modestly increased risk of CHD among oil spill workers exposed to higher levels of THC and BTEX-H, with the strongest associations observed in the highest quintile of each exposure; however, we did not observe clear exposure–response trends. The positive associations were consistent with evidence from ambient air pollution research indicating that exposure to these agents at levels below occupational guidelines may induce adverse cardiovascular effects. To our knowledge, our study is the first to evaluate the relationship between exposure to individual crude oil chemicals and risk of CHD in the occupational setting. We further showed stronger associations in some subgroups, i.e., ever smokers, workers who had high school education or less, and workers who were not obese. Additional research is needed in other populations and settings to confirm these study findings.

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